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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/541,191	10/11/95	KAYYEM J	A-62629/RFT

EXAMINER

HM12/0511

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EXAMINER	
JONES, D	
ART UNIT	PAPER NUMBER
1616	20

DATE MAILED: 05/11/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/5/99 ; 3/15/99

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-22 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-22 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

★ U.S. GPO: 1998-421-632/40206

RESPONSE TO APPLICANT'S ARGUMENTS

1. The Applicant's arguments filed 3/15/99 (Paper No. 19) to the rejection of claims 1-22 made by the Examiner under 35 U.S.C. 103 and double patenting have fully considered and deemed non-persuasive. Therefore, all outstanding rejections are MAINTAINED for the reasons set forth below.

Statutory Double Patenting

2. The statutory type (35 U.S.C. 101) double patenting rejection of claims 1-4, 6-10, 12-13, 16, and 22 over claims 1-8, 12, and 21-23 of copending Serial No. 08/321,552 is **MAINTAINED** for the reasons set forth in the Office Action mailed 7/7/97, Paper No. 9.

Obviousness-type Double Patenting

3. The obviousness-type double patenting rejection of claims 5, 11, 14-15, and 17-21 over claims 9-11, 24-27, and 35-38 of copending Serial No. 08/321,552 is **MAINTAINED** for the reasons set forth in the Office Action mailed 7/7/97, Paper No. 9.

103 Rejection

4. The **rejection** of claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem., Vol. 266, No. 22, pp. 14338-14342, August 5, 1991) in view of Kornguth et al (US Patent No. 5,230,883) is **MAINTAINED** in the Office Action mailed 9/11/98, Paper No. 16, and those disclosed below.

I. Applicant asserts that Wu et al does not teach or suggest the addition of a physiological agent such as a therapeutic agent or contrast agent and Kornguth et al does not teach or suggest the use of a second polymer, nor does Kornguth teach or suggest the use of a cell targeting moiety.

As stated in the Office Action mailed 9/11/98, Wu et al is not relied upon as teaching the inclusion of an MRI agent, but the concept of targeting an agent of interest to a cell. Thus, Wu et al indicates that one of

ordinary skill in the art recognizes that the use of multiple polymers of DNA and polylysine linked to a specific binding agent may be used to deliver DNA to a specific target cell. Hence, Wu et al set the precedent for the use of polylysine, a positive charged agent, coupled to a cell specific binding agent. Furthermore, as stated in the Office Action mailed 9/11/98, Kornguth et al is relied upon for its teachings of coupling polylysine to a linking group and imaging agent or chemotherapeutic agent.

II. Applicant's asserts that there is no motivation to combine Wu et al and Kornguth et al.

Motivation for combining the references is based upon the critical teachings of Kornguth et al in the context of Wu et al wherein each element of Applicant's invention with the exception of an imaging agent is disclosed. However, since it is recognized in the art that polylysine is useful as a carrier molecule of components of interest including cell targeting molecules and contrast agents, one would be motivated to use polylysine conjugates to deliver nucleic acids as set forth in Applicant's claims 2-3 and 8 for delivery of imaging agents.

III. Applicant asserts that Kornguth et al teaches away from the instant invention because the addition of a nucleic acid which has a high net negative charge to the polylysine would substantially decrease or eliminate the targeting function of the polylysine and the reference does not teach or suggest the use of cell targeting moieties.

The Examiner respectfully points out the following.

(1) On pages 7-8 of specification, bridging paragraph, it is disclosed that the preferred first polymeric molecule is a nucleic acid which includes DNA;

(2) On pages 9-10 of specification, bridging paragraph, it is disclosed that the polyanion and the polycation will have sufficient charge so that when combined, the two polymeric molecules form a polycomplex under physiological complex. Furthermore, it is disclosed that generally after complex formation, the polycomplexes are approximately electrically neutral since electroneutrality is generally necessary to achieve high transfection efficiency (the specification cites Wagner et al, 1991, as evidence of such statement).

(3) On page 10 of specification, lines 9-26, it is disclosed that an especially preferred polycation is polylysine. Furthermore, it is disclosed that (a) when polylysine is used as the second polymeric molecule, the -NH2 groups of the lysine side chain at high ~~PH~~ pH serve as strong nucleophiles for multiple attachment of activated chelating agents; (b) at high pH, the lysine monomers are coupled to the physiological agents under condition that yield on average 5 - 20% monomer substitution; (c) at physiologic pH to low pH, the remaining unlabeled positively charged lysine facilitate nucleic acid binding; and (d) the instant invention takes advantage of both the polycationic and polynucleophilic nature of polyamines such as lysine.

Hence, based on the disclosure of Applicant's specification, it is unclear how Kornguth et al teaches away from the instant invention by the addition of a nucleic acid to polylysine because such statement 'appears' to contradict what is claimed and disclosed in Applicant's specification.

IV. Applicant's asserts that the addition of asialoglycoprotein from Wu et al to the Kornguth et al compositions *could result* in a loss of targeting in Kornguth et al since the complexes would also be taken up by hepatocytes.

The Examiner agrees that the addition of the asialoglycoprotein from Wu et al in combination with the compositions of Kornguth et al may result in a loss of targeting. However, it is also quite possible that

the addition of the asialoglycoprotein *may not* result in a loss of targeting specificity. Thus, without evidence (i.e., data) that the addition of asialoglycoprotein from Wu et al to the Kornguth et al compositions definitely results in a loss of targeting in Kornguth et al compositions, it is believed that the teachings of Kornguth et al in combination with Wu et al render Applicant's invention obvious.

V. Applicant asserts that the complexes of the invention show a surprising and unexpected benefit over the complexes of the prior art when the Kayyem et al (Current Bio., 2,:615-620 (1995)) document and in particular Figure 3 are reviewed.

In regards to Applicant's assertions regarding unexpected result, the Examiner's position is that Applicant has shown unexpected result when DNA/Tf/Gd-DTPA/PL is utilized (see Figures 2 and 3 of the instant invention). However, the data does not read on any possible four-component system, especially since the number of possible first polymeric molecule, second polymeric molecule, cell targeting moiety, and contrast agent combinations as claimed is unlimited. Hence, if Applicant limits the invention to the embodiment for which unexpected results are shown, then, the claims would be allowable (Applicant would also have to respond to the statutory and obviousness-type double patenting rejections).

5. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to the Group 1600 fax machine at (703) 308-4556. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30; November 15, 1989.

6. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. Examiner Jones can generally be reached from Monday through Friday between 7:00 a.m. and 3:30 p.m. If the Examiner cannot be reached, questions may be addressed to her supervisor, Jose Dees, whose phone number is (703) 308-4628.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

DLJ
May 7, 1999

JOSE' G. DEES
SUPERVISORY PATENT EXAMINER
1616